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(54)【発明の名称】　医療用ポリスルホン中空糸膜

(57)【要約】

【目的】　膜表面への血液蛋白、血小板等の付着が少なく、ろ過速度の経時変化の小さい中空糸膜であり、なおかつ、安全性にも優れた医療用のポリスルホン系樹脂中空糸膜を提供する。

【構成】　ポリスルホンとポリビニルピロリドンによって構成された中空糸膜において特に血液が直接接触する中空糸膜内表面でのポリビニルピロリドンの存在率を２０％～５０％とすることを特徴とする医療用ポリスルホン中空糸膜。

【特許請求の範囲】

【請求項１】　ポリスルホン系樹脂とポリビニルピロリドンからなる中空糸膜であって，膜内表面におけるポリビニルピロリドンの存在率が２０％以上、５０％以下であることを特徴とする医療用ポリスルホン中空糸膜。

【発明の詳細な説明】

【０００１】

【産業上の利用分野】本発明はポリスルホン中空糸膜に関するものであり、特に腎不全の治療を目的とした血液透析や血液ろ過に好適な医療用ポリスルホン中空糸膜に関する。

【０００２】

【従来の技術】腎不全の治療のために現在各種の人工腎臓が使用されているが、これらの大部分は中空糸膜を用いて血液透析や血液ろ過を行うことで尿素を代表とする血液中の老廃物を除去するためのものである。従って、血液は膜と接触しなければならないために膜の素材としては、セルロース、セルロースアセテート、ポリアクリロニトリル、ポリスルホン、ポリメチルメタクリレート、エチレンービニルアルコール共重合体等の生体に対して安全な素材が用いられている。

【０００３】一方、血液透析や血液ろ過は４時間から５時間の治療時間を必要とするため、治療を安定に行うには安定した除水能力が求められるが、血液蛋白等の膜表面への付着が多いと経時的に除水能力が低下してくるために、血液蛋白の付着あるいは血小板を代表とする血球成分の付着が少ない抗血栓性、生体適合性に優れた中空糸膜が望まれる。

【０００４】こうした課題を解決する手段としては、一般的に膜に親水性をもたせることが有用だと考えられており、例えば、特公平２－１８６９５号公報には疎水性高分子と親水性高分子であるポリビニルピロリドンからなる膜においてポリビニルピロリドンの膜中での含有率を５％から７０％とすることで膜の親水性を高め、生体適合性、抗血栓性を向上させる方法が開示されているが、膜の組成比に関してのみの記載であり、血液が直接接触し医療用に用いられる中空糸膜の抗血栓性、生体適合性を決定するのにもっとも重要となる中空糸膜内表面に関してはなんら記載されていない。

【０００５】一方、特開昭６１－４０２号公報や特開昭６２－３８２０５号公報には緻密層側だけに親水性高分子を含む膜が、また特開平４－３００６３６号公報には中空糸膜の内表面側にポリビニルピロリドンが偏在した膜が開示されているが、ともに膜表面そのもの、すなわち血液に接触する表面近傍部に親水性高分子が存在する事の記載のみであり、その性質についての具体的な記載はなんらなされていない。

【０００６】

【発明が解決しようとする課題】本発明は抗血栓性、生体適合性に優れた血液透析、血液ろ過に好適な医療用のポリスルホン中空糸膜を提供することを目的とするものである。

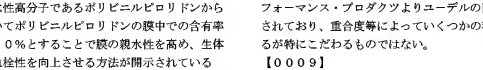
【０００７】

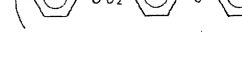
【課題を解決するための手段】抗血栓性、血液適合性に優れた医療用中空糸膜を提供するために本発明者らは鋭意検討の結果、本発明を完成するに至ったものである。すなわち本発明は、ポリスルホン系樹脂とポリビニルピロリドンからなる中空糸膜であって、内表面におけるポリビニルピロリドンの存在率が２０％以上、５０％以下であることを特徴とする医療用のポリスルホン中空糸膜である。

【０００８】以下に本発明を詳細に説明する。ポリスルホン系樹脂とは、スルホン結合を有する高分子化合物の総称であり特に規定するものではないが、例をあげると下記（１）式または（２）式で示されるポリスルホン系樹脂が広く市販されており入手も容易なため好ましく、中でも（１）式で示す化学構造を持つポリスルホン樹脂がよい。この構造を持つポリスルホン樹脂はアモコ・パフォーマンス・プロダクツよりユーデルの商品名で市販されており、重合度等によっていくつかの種類が存在するが特にこだわるものではない。

【０００９】

【化１】





【００１０】また、ポリビニルピロリドンは、例えばアイ・エス・ピーからプラスドンの商品名で各種分子量の

ポリビニルピロリドンが市販されており、本発明においてはどの分子量のポリビニルピロリドンをも使用することが可能である。分子量が大きいほど膜中へのポリビニルピロリドンの残留率が大きくなるため、好ましくは分子量３００，０００以上のポリビニルピロリドンを使用する。

【００１１】中空糸膜の製膜に際しては従来より一般的に知られている技術である乾湿式製膜技術が使用できる。乾湿式製膜を行うための製膜原液としては、ポリスルホン系樹脂とポリビニルピロリドンの両者を共通に溶解する溶剤に溶解混和した溶液が用いられる。該溶剤としては特に規定するものではないが、Ｎ，Ｎ－ジメチルアセトアミド，Ｎ，Ｎ－ジメチルフォルムアミド、Ｎ－メチルピロリドン、ジメチルスルフォキシド等の溶剤が溶解性も高く、入手も容易であるため箇倭に使用できる。中でもポリスルホンに対する溶解性や生体に対する安全性、コスト等を考えるとＮ，Ｎ－ジメチルアセトアミドがもっとも好ましい。これらの溶剤は単独で使用できることはもちろんであるが、ポリマー対する溶解性を調整するために２種またはそれ以上の種類の溶剤を混合しても使用することができる。

【００１２】該ポリスルホン系樹脂の濃度は、低すぎると膜形成が困難となり膜強度が弱くなってしまったり、高すぎると紡糸性が悪くなったり孔径が小さくなる等の現象が生じてくるので、１２～２５重量%、中でも１５～２０重量%、さらには１６～１８重量%であることが好ましいが、この範囲に限定される事はなく、目的とする中空糸膜の性状によってはこの範囲より低くすることも高くすることもできる。

【００１３】製膜原液中に添加したポリビニルピロリドンは、膜が形成される過程においてその一部が膜中に残存する。その残存割合は、ポリビニルピロリドンの分子量や紡糸条件により変化してくるので、ポリビニルピロリドンの最適な濃度は変化してくるが、一般的には１～２０重量%がよく、好ましくは２～１５重量%、さらに好ましくは３～１０重量%がよい。ポリビニルピロリドンは分子量が大きくなるにつれて膜中に残存しやすくなるため、ポリビニルピロリドンの分子量が大きい場合はその濃度は低くてもよい。例えばポリビニルピロリドンの分子量が３００，０００以上の時には１～１５重量%、特に３～７重量%である事が好ましい。

【００１４】一般的に１重量%より低いと膜中に残存するポリビニルピロリドンが少なくなりすぎるために中空糸膜内表面に存在するポリビニルピロリドンは２０%以下となってしまい、親水化が不十分となって血液蛋白の付着が激しくなり安定的な除水性能が得られなくなる。また、２０重量%よりも高いと製膜原液の粘性が高くなりすぎて製膜が困難となるため、ポリビニルピロリドンの添加量は上記範囲内で適宜設定すべきである。

【００１５】また、該製膜原液の粘度調整あるいは目的とする中空糸膜の孔径制御等の為に、テトラエチレングリコール、プロピレングリコール、エタノール、イソプロピルアルコール、グリセリン、水等の非溶剤を加えることも可能であり、その種類、添加量等については目的とする中空糸膜の性状に応じて適宜選択できる。中空糸膜の製膜はチューブインオリフィス型の紡口を用い、その精部から該製膜原液を押し出すと同時に、芯部からは内部凝固液を押し出し、５ｃｍから１ｍの距離を走行させて後、凝固溶中へ浸せきさせ、その後巻き取ってやれば良い。

【００１６】内部凝固液及び凝固溶液としては水を主体とした液が用いられるが、目的とする中空糸膜の性状を発現するためにポリスルホン樹脂の溶剤と水の混合液を用いることができる。製膜に際して重要なのは製膜時の原液粘性であり１，５００～６，０００センチポイズであることが好ましいが、さらに好ましいのは３，０００～４，５００センチポイズとすることである。というのもポリビニルピロリドンは水溶性であるため膜凝固時にその一部が凝固溶中へ溶出してくるが、原液粘性を高くすることでポリビニルピロリドンの拡散移動が抑えられ膜中に残存しやすくなるためである。

【００１７】さらに重要なのは空中部の走行距離であるが、その理由として膜の形成すなわち凝固が充分に終了しておらず、ポリビニルピロリドンがまだ拡散移動できる状態で中空糸が凝固溶中に浸せきされると、ポリビニルピロリドンは凝固溶中へ溶出してしまい、ポリビニルピロリドンは膜中に残らなくなってしまうからである。

【００１８】従って、紡口より押し出された製膜原液は凝固溶中に浸せきされるまでの間に充分に凝固していることが好ましく、そのためには製膜原液が紡口より押し出されてから凝固溶中に浸せきされるまでの時間が０．１秒以上、さらには０．３秒以上であることが好ましい。このためには紡糸速度が５０ｍ／分の場合には空中部の距離はおおよそ８ｃｍ以上、さらには２５ｃｍ以上とするのがよい。またその上限については必ずしも規定されるものではなく大きくするほど好ましいが、あまり大きくすると糸切れが発生しやすくなるため１００ｃｍを越えない範囲であるのがよい。

【００１９】凝固溶へ浸せきされた中空糸膜は必要に応じてさらに水洗溶中で水洗を行った後巻取を行う。得られた中空糸膜は未洗浄の残溶剤を除去するためにさらに温水等で洗浄すればよく、必要に応じてグリセリン等の孔径保持剤を付着させて乾燥することもできる。このようにして得られた中空糸膜は原表面のポリビニルピロリドン存在率が２０%以上、５０%以下となっており、抗血栓性、生体適合性に優れ、蛋白、血小板等の膜面付着も軽徴であった。この膜は安定した除水能力を有しており血液透析、血液ろ過等の治療を安定に実施するために大きな効果を発揮するものである。

【００２０】ところで、ポリビニルピロリドンの膜表面

での存在比を２０％以上とすることでなぜ安定した除水能力が得られるのかについての詳細は不明であるが、本来蛋白等を吸着しやすい疎水性であるポリスルホンの表面部を親水性の高分子であるポリビニルピロリドンがおおいかくすのに必要な存在率が２０％以上であり、その結果として膜表面は充分に親水化されているので膜表面への蛋白等の吸着性が弱められ安定した除水能力が得られるものと予想される。

【００２１】また、ポリビニルピロリドンの膜表面での存在率が５０％より大きいと膜表面はより一層親水化されているので性能は安定しているのであるが、その反面血液透析時等においてポリビニルピロリドンが血液中に溶出してくる危険性が伴うために安全性の上で問題がでてくる可能性があるのでポリビニルピロリドンの存在率は５０％以下であることが好ましい。

【００２２】なお本発明でいう膜表面でのポリビニルピロリドンの存在率とは血液が膜と接触する極表層部での存在率であり、具体的にはエックス線光量子スペクトル（Ｘ－ｒａｙ　ｐｈｏｔｏｅｌｅｃｔｒｏｎ　ｓｐｅｃｔｒｏｓｃｏｐｙ，以下ＸＰＳ）により求めた膜表面部での窒素含量と硫黄含量から求めた存在率をいうものであり、ポリスルホン樹脂が（１）式の構造であるときには（３）式により計算で求める事ができる。

【００２３】

【数１】

$$\text{ポリビニルピロリドン存在率（\%）} = \frac{\text{窒素原子数}\times 111}{\text{窒素原子数}\times 111 \;+\; \text{硫黄原子数}\times 442}\times 100 \quad \cdots(3)$$

【００２４】

【実施例】以下に実施例および参考例をもとに本発明を詳細に説明する。

【００２５】

【実施例１】ポリスルホン樹脂（アモコ・パフォーマンス・プロダクツ，Ｐ－１７００）１８部，ポリビニルピロリドン（アイ・エス・ピー，プラスドンＫ－９０，分子量３６０００）５部，Ｎ，Ｎ－ジメチルアセトアミド７７部を均一溶解した。この原液は４５度で３，８００センチポイズの粘度を有していた。チューブインオリフィス型の中空紡口を用いて内部凝固液として５０％の濃度のＮ，Ｎ－ジメチルアセトアミド水溶液を吐出させながら，４５度に保温した状態でこの製膜原液を同時に吐出させた。該原液は４０ｃｍ下方にもうけられた温度５０度の水浴中に浸せきされた後５０ｍ／ｍｉｎの速度で巻き取られた。

【００２６】得られた中空糸膜は内径０．１９５mm、外径０．３１０mm、透水性能２４５ｍｌ／Ｈｒ・m^2・ｍｍＨｇであり、ＸＰＳにより求めた膜表面部でのポリビニルピロリドン存在率は３５％であった。得られた中空糸膜を用いて有効膜面積０．０２m^2のミニモジュールを作成し、線速１ｃｍ／秒、ろ過圧２００ｍｍＨｇの状態で総蛋白濃度５．８ｇ／Ｌの牛血しょうを流しろ過速度の経時変化を見たところ、変化は軽微であった。

【００２７】さらに、得られた中空糸膜に対して透析型人工腎臓承認基準に基づいて安全性試験を実施したところ全項目合格であった。それらの結果を表１に示す。

【００２８】

【比較例１】ポリスルホン（Ｐ－１７００）１８部、ポリビニルピロリドン（Ｋ－９０）０．５部、Ｎ，Ｎ－ジメチルアセトアミド８１．５部の比率で均一溶解し、４５度で７５０センチポイズの粘度を有する製膜原液を得た。この製膜原液を用いて、内部凝固液を６５％のＮ，Ｎ－ジメチルアセトアミド水溶液とする以外は実施例１と同様にして中空糸膜を得た。

【００２９】この中空糸膜は内径０．２０８mm、外径０．３２７mm、透水性能１８３ｍｌ／Ｈｒ・m^2・ｍｍＨｇであり、膜表面のポリビニルピロリドン存在率は１８％であった。得られた中空糸膜を用いて実施例１と同様の試験を実施した。安全性試験には合格したが、ろ過速度の経時変化が大きく安定した除水性能が得られなかった。

【００３０】それらの結果を表１に示す。

【００３１】

【比較例２】ポリスルホン（Ｐ－１７００）１８部、ポリビニルピロリドン（Ｋ－１５）２５部、Ｎ，Ｎ－ジメチルアセトアミド５７部の比率で均一溶解し、４５度で７，６００センチポイズの製膜原液を得た。この製膜原液を用いて、内部凝固液を水とする以外は実施例１と同様にして中空糸膜を得た。

【００３２】この中空糸膜は内径０．１９２mm、外径０．２９８mm、透水性能３７０ｍｌ／Ｈｒ・m^2・ｍｍＨｇであり、膜表面のポリビニルピロリドン存在率は５５％であった。参考例４で得られた中空糸膜を用いて実施例２、３と同様の試験を実施したところ、ろ過速度の経時変化は小さく安定した除水性能が得られたが、安全性試験における紫外線吸収スペクトルの項目で不合格となった。

【００３３】それらの結果を表１に示す。

【００３４】

【表１】

使用した中空糸膜	ろ過速度（ml／Hr・m² ・mmHg）					溶出物試験
	15分後	1時間後	2時間後	3時間後	4時間後	
実施例1	22．5	23．4	22．3	21．8	21．3	合格
比較例1	18．4	17．8	16．2	14．4	12．6	合格
比較例2	24．7	23．5	23．7	22．9	22．9	不合格

【0035】

【発明の効果】本発明によれば、ポリスルホン中空糸膜の膜内表面がポリビニルピロリドンによって親水化され、その存在率が20%～50%となっているために、中空糸膜内表面への蛋白や血小板等の付着が抑制され目詰まりがおこりにくくなる。そのため安定した除水能力が維持できるので血液透析や血液ろ過療法を安定に施行できるとともに、安全性にも優れた医療用のポリスルホン膜を提供しうる。

I. PATENT ABSTRACTS OF JAPAN

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ASAHI MEDICAL CO LTD
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YAMADA MASAKAZU

(54) **POLYSULFONE HOLLOW YARN MEMBRANE FOR MEDICAL PURPOSE**

(57)Abstract:
PURPOSE: To provide the polysulfone resin hollow yarn membrane for medical purposes which is a hollow yarn membrane having less adhesion of blood proteins, platelets, etc., on the membrane surfaces and to be less changed in filtration rate with the lapse of time and has excellent safety.
CONSTITUTION: This polysulfone hollow yarn membrane for medical purposes is the hollow yarn membrane composed of polysulfone and polyvinyl pyrrolidone and has 20 to 50% presence ratio of the polysulfone on particulrly the inside surface of the hollow yarn membrane with which blood comes into contact directly.

LEGAL STATUS

[Date of request for examination]	09.02.2000
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[Date of extinction of right]

CLAIMS

[Claim(s)]
[Claim 1] The medical-application polysulfone hollow fiber characterized by being the hollow fiber which consists of polysulfone system resin and a polyvinyl pyrrolidone, and the abundance of the polyvinyl pyrrolidone in a film internal surface being 20% or more and 50% or less.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to a polysulfone hollow fiber, and relates to the suitable medical-application polysulfone hollow fiber for hemodialysis and blood filtration especially aiming at the therapy of renal failure.
[0002]
[Description of the Prior Art] Although the artificial kidney of current various kinds is used for the therapy of renal failure, these most are for removing the wastes in the blood which makes a urea representation by performing hemodialysis and blood filtration using a hollow fiber. Therefore, in order that blood may contact the film, as a membranous material, the safe material is used to living bodies, such as a cellulose, cellulose acetate, a polyacrylonitrile, polysulfone, polymethylmethacrylate, and an ethylene-vinylalcohol copolymer.
[0003] On the other hand, if there is much adhesion on film front faces, such as blood protein, in order that the dewatering capacity stabilized in stability is searched for for treating since hemodialysis and blood filtration need 4 to 5 hours therapy time amount, but dewatering capacity may decline with time, a hollow fiber adhesion of the corpuscle component which makes adhesion of blood protein or a platelet representation excelled [hollow fiber] in few anti-thrombus nature and biocompatibility is desired.
[0004] It is thought that it is useful to give a hydrophilic property to the film generally as a means to solve such a technical problem. For example, a membranous hydrophilic property is raised to JP,2-18695,B by making content in the inside of the film of a polyvinyl pyrrolidone into 5 to 70% in the film which consists of a polyvinyl pyrrolidone which are a hydrophobic giant molecule and a hydrophilic giant molecule. Although the method of raising biocompatibility and anti-thrombus nature is indicated, the hollow fiber internal surface which is the publication only about a membranous presentation ratio and becomes the most important for determining the anti-thrombus nature of a hollow fiber by which blood contacts directly and is used for medical application, and biocompatibility is not indicated at all.

[0005] the film which contains a hydrophilic giant molecule in JP,61-402,A or JP,62-38205,A on the other hand only at a compact layer side -- moreover, although the film with which the polyvinyl pyrrolidone was unevenly distributed in the internal-surface side of a hollow fiber is indicated by JP,4-300636,A, it is only the publication of a hydrophilic giant molecule existing in the section near the front face which both contacts the film front face, i.e., blood, itself, and the concrete publication about the property is not made at all.

[0006]

[Problem(s) to be Solved by the Invention] This invention aims at offering the polysulfone hollow fiber of the suitable medical application for hemodialysis and blood filtration excellent in anti-thrombus nature and biocompatibility.

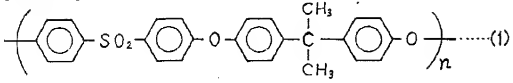
[0007]

[Means for Solving the Problem] In order to offer the medical-application hollow fiber excellent in anti-thrombus nature and haemocompatibility, this invention persons come to complete this invention wholeheartedly as a result of examination. That is, this invention is a hollow fiber which consists of polysulfone system resin and a polyvinyl pyrrolidone, and is the polysulfone hollow fiber of the medical application characterized by the abundance of the polyvinyl pyrrolidone in an internal surface being 20% or more and 50% or less.

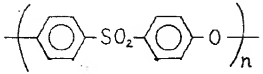
[0008] This invention is explained below at a detail. Although polysulfone system resin is especially the generic name of the high molecular compound which has sulfone association and it does not specify, when an example is given, the polysulfone system resin shown by following the (1) type or (2) formulas is marketed widely, since acquisition is also easy, it is desirable, and polysulfone resin with the chemical structure shown by (1) formula especially is good. The polysulfone resin with this structure is marketed by the trade name of you Dell from the Amoco performance products, and especially although some classes exist with polymerization degree etc., it is not scrupulous.

[0009]

[Formula 1]



(1)



(2)

[0010] Moreover, the polyvinyl pyrrolidone of various molecular weight is marketed by a plus boss's trade name for example, from insertion sequence Py, and a polyvinyl pyrrolidone can use the polyvinyl pyrrolidone of every molecular weight in this invention. Since the residual percentage of the polyvinyl pyrrolidone to the inside of the film becomes large so that molecular weight is large, a with a molecular weight of 300,000 or more polyvinyl pyrrolidone is used preferably.

[0011] The dryness-and-moisture type film production technique which is a technique generally known from before on the occasion of film production of a hollow fiber can be used. The solution which carried out dissolution mixing is used for the solvent which dissolves both polysulfone system resin and polyvinyl pyrrolidone in common as a film production undiluted solution for performing dryness-and-moisture type film production. Although it does not specify especially as this solvent, it is high, and since acquisition is also easy, solvents, such as N,N-dimethylacetamide, N, and N-dimethyl formamide, N-methyl pyrrolidone, and dimethyl sulfoxide, can also use solubility simple. N,N-dimethylacetamide is the most desirable when safety, cost, etc. to the solubility and living body to polysulfone are considered especially. Although these solvents can be used of course independently, it can be used even if it mixes the solvent of the class beyond two sorts or it, in order to adjust the solubility which carries out a polymer pair.
[0012] Since film formation will become difficult if the concentration of this polysulfone system resin is too low, and film reinforcement becomes weak, or spinning nature will worsen if too high, or phenomena, like an aperture becomes small arise Although it is desirable that they are 15 - 20 % of the weight and further 16 - 18 % of the weight especially 12 to 25% of the weight, it can also make it high to make it lower than this range depending on the description of the hollow fiber which it is not limited to this range and made into the purpose.
[0013] A part of the polyvinyl pyrrolidone added in the film production undiluted solution remains in the film in the process in which the film is formed. Since the residual rate changes with the molecular weight and the spinning conditions of a polyvinyl pyrrolidone, although the optimal concentration of a polyvinyl pyrrolidone changes, generally its 1 - 20 % of the weight is good, and 3 - 10 % of the weight is still more preferably good [concentration] two to 15% of the weight preferably. Since a polyvinyl pyrrolidone becomes easy to remain in the film as molecular weight becomes large, the concentration may be low when the molecular weight of a polyvinyl pyrrolidone is large. For example, especially when the molecular weight of a polyvinyl pyrrolidone is 300,000 or more, it is desirable that it is 3 - 7 % of the weight one to 15% of the weight.
[0014] Since the polyvinyl pyrrolidone which remains in the film will decrease too much if lower generally than 1 % of the weight, the polyvinyl pyrrolidone which exists in a hollow fiber internal surface becomes 20% or less, hydrophilization becomes inadequate, adhesion of blood protein becomes intense, and the stable dewatering engine performance is no longer obtained. Moreover, since the viscosity of a film production undiluted solution will become high too much and film production will become difficult if higher than 20 % of the weight, the addition of a polyvinyl pyrrolidone is within the limits, and should be set [above-mentioned] up suitably.
[0015] Moreover, for the aperture control of a hollow fiber made into the viscosity control or the purpose of this film production undiluted solution, it is also possible to add nonsolvents, such as tetraethylene glycol, propylene glycol, ethanol, isopropyl alcohol, a glycerol, and water, and it can choose suitably according to the description of the hollow fiber made into the purpose about the class and an addition. What is necessary is for film production of a hollow fiber to extrude internal coagulation liquid, and to make it run the distance of 1m from 5cm, and to carry out the dipping of it and just to roll it round after that the back and into a coagulation bath, from a core part, at the same time it extrudes this film production undiluted solution from the sheath using the spinning port of a tube in orifice mold.
[0016] Although the liquid which made water the subject as internal coagulation liquid and coagulation bath liquid is used, in order to discover the description of the hollow fiber made into

the purpose, the solvent of polysulfone resin and the mixed liquor of water can be used. It is that still more desirable one considers as 3,000 to 4,500 centipoise on the occasion of film production although it is desirable that it is the undiluted solution viscosity at the time of film production, and is 1,500 to 6,000 centipoise as for important one. That is, although the part is eluted into a coagulation bath at the time of film coagulation since a polyvinyl pyrrolidone is water solubility, it is because the spreading diffusion of a polyvinyl pyrrolidone is suppressed by making undiluted solution viscosity high and it becomes easy to remain in the film.

[0017] Although the mileage of the air section is still more important, when the dipping of the hollow filament is carried out into a coagulation bath in the condition that it is not fully completed as the reason, membranous formation, i.e., coagulation, but the spreading diffusion of the polyvinyl pyrrolidone can still be carried out, it is because a polyvinyl pyrrolidone is eluted into a coagulation bath and a polyvinyl pyrrolidone stops remaining into the film.

[0018] Therefore, as for the film production undiluted solution extruded from the spinning port, it is desirable to fully have solidified, by the time a dipping is carried out into a coagulation bath, and it is desirable that time amount after a film production undiluted solution is extruded from a spinning port for that purpose until a dipping is carried out into a coagulation bath is 0.1 seconds or more and 0.3 more seconds or more. When for that a spinning rate is a part for 50m/, the distance of the air section is good to be about referred to as 8cm or more and 25 morecm or more. Moreover, although it is so desirable that it is not necessarily specified and enlarges about the upper limit, since it will become easy to generate the thread breakage if it enlarges not much, it is good that it is the range which does not exceed 100cm.

[0019] The hollow fiber by which the dipping was carried out to the coagulation bath rolls round, after rinsing in a wash bath further if needed. In order to remove a non-washed residual solvent, that what is necessary is for warm water etc. just to wash further, the obtained hollow fiber can make aperture hold-back agents, such as a glycerol, able to adhere if needed, and can also be dried. Thus, the polyvinyl-pyrrolidone abundance on the front face of the film had become 20% or more and 50% or less, the obtained hollow fiber was excellent in anti-thrombus nature and biocompatibility, and its film surface adhesion of protein, a platelet, etc. was also slight. This film demonstrates big effectiveness, in order to have the stable dewatering capacity and to treat hemodialysis, blood filtration, etc. to stability.

[0020] By the way, although the detail about the dewatering capacity stabilized why by making the abundance ratio on the front face of the film of a polyvinyl pyrrolidone into 20% or more being acquired is unknown Abundance required for the polyvinyl pyrrolidone which is the giant molecule of a hydrophilic property to cover the surface section of the polysulfone which is the hydrophobicity which is originally easy to adsorb protein etc., and hide it is 20% or more. Since hydrophilization of the film front face is fully carried out as the result, it is expected that the dewatering capacity by which adsorbent [of the protein on the front face of the film etc.] was weakened and stabilized is acquired.

[0021] Moreover, since a problem may crop up on safety in order that the engine performance is stable since hydrophilization of the film front face is further carried out if the abundance on the front face of the film of a polyvinyl pyrrolidone is larger than 50%, but on the other hand the danger that a polyvinyl pyrrolidone will be eluted in blood in the time of hemodialysis etc. may follow, as for the abundance of a polyvinyl pyrrolidone, it is desirable that it is 50% or less.

[0022] In addition, the abundance of the polyvinyl pyrrolidone on the front face of the film as used in the field of this invention say the abundance calculated from the nitrogen content and sulfur content in the film surface section for which blood be the abundance in the pole surface

section in contact with the film, and it specifically asked with the X ray photon spectrum (X-ray photoelectron spectroscopy, henceforth, XPS), and when polysulfone resin be the structure of (1) type, it can ask by count by (3) types.

[0023]

[Equation 1]

ポリビニルピロリドン存在率（%）

$$= \frac{\text{窒素原子数} \times 1\,1\,1}{\text{窒素原子数} \times 1\,1\,1 \quad + \quad \text{硫黄原子数} \times 4\,4\,2} \times 1\,0\,0 \qquad \cdots (3)$$

[0024]

[Example] This invention is explained based on an example and the example of reference below at a detail.

[0025]

[Example 1] The homogeneity dissolution of the polysulfone resin (Amoco performance products, P-1700) 18 section, the polyvinyl-pyrrolidone (insertion sequence Py, plus boss K-90, molecular weight 360000) 5 section, and the N,N-dimethylacetamide 77 section was carried out. This undiluted solution had the viscosity of 3,800 centipoises at 45 degrees. Coincidence was made to breathe out this film production undiluted solution in the condition of having kept it warm at 45 degrees, making the N,N-dimethylacetamide water solution of 50% of concentration breathe out as internal coagulation liquid using the hollow spinning port of a tube in orifice mold. This undiluted solution was rolled round at the rate of back 50 m/min by which the dipping was carried out during the water bath of 50 temperature already kicked caudad 40cm.

[0026] The obtained hollow fibers were permeable ability 245 ml/Hr-m2, and [the bore of 0.195mm, the outer diameter of 0.310mm, and] mmHg, and the polyvinyl-pyrrolidone abundance in the film surface section for which it asked by XPS was 35%. The obtained hollow fiber is used and it is 2 0.02m of effective film surface products. Change was slight, when the mini module was created and aging of sink filtration velocity was seen for the cow plasma of total protein concentration 5.8 g/L in the state of the linear velocity of 1cm/second, and filtration pressure 200mmHg.

[0027] Furthermore, when the safety test was carried out based on dialysis mold artificial-kidney acknowledgement criteria to the obtained hollow fiber, they were all item success. Those results are shown in Table 1.

[0028]

[The example 1 of a comparison] The film production undiluted solution which carries out the homogeneity dissolution by the ratio of the polysulfone (P-1700) 18 section, the polyvinyl-pyrrolidone (K-90) 0.5 section, and the N,N-dimethylacetamide 81.5 section, and has the viscosity of 750 centipoises at 45 degrees was obtained. The hollow fiber was obtained like the example 1 using this film production undiluted solution except using internal coagulation liquid as 65% of N,N-dimethylacetamide water solution.

[0029] This hollow fiber was permeable ability 183 ml/Hr-m2, and [the bore of 0.208mm, the outer diameter of 0.327mm, and] mmHg, and the polyvinyl-pyrrolidone abundance on the front face of the film was 18%. The same trial as an example 1 was carried out using the obtained hollow fiber. Although the safety test was passed, the dewatering engine performance by which aging of filtration velocity was stabilized greatly was not obtained.

[0030] Those results are shown in Table 1.

[0031]
[The example 2 of a comparison] The homogeneity dissolution was carried out by the ratio of the polysulfone (P-1700) 18 section, the polyvinyl-pyrrolidone (K-15) 25 section, and the N,N-dimethylacetamide 57 section, and the film production undiluted solution of 7,600 centipoises was obtained at 45 degrees. The hollow fiber was obtained like the example 1 using this film production undiluted solution except using internal coagulation liquid as water.
[0032] This hollow fiber was permeable ability 370 ml/Hr-m2, and [the bore of 0.192mm, the outer diameter of 0.298mm, and] mmHg, and the polyvinyl-pyrrolidone abundance on the front face of the film was 55%. When the same trial as examples 2 and 3 was carried out using the hollow fiber obtained in the example 4 of reference, aging of filtration velocity became a rejection by the item of the ultraviolet absorption spectrum in a safety test, although the dewatering engine performance stabilized small was obtained.
[0033] Those results are shown in Table 1.
[0034]
[Table 1]

使用した中空糸膜	ろ過速度（ml／Hr・m²・mmHg）					溶出物試験
	15分後	1時間後	2時間後	3時間後	4時間後	
実施例1	22．5	23．4	22．3	21．8	21．3	合格
比較例1	18．4	17．8	16．2	14．4	12．6	合格
比較例2	24．7	23．5	23．7	22．9	22．9	不合格

[0035]
[Effect of the Invention] Since according to this invention hydrophilization of the film internal surface of a polysulfone hollow fiber is carried out by the polyvinyl pyrrolidone and the abundance has become 20% - 50%, adhesion of the protein to a hollow fiber internal surface, a platelet, etc. is controlled, and it is hard coming to start blinding. Therefore, since the stable dewatering capacity is maintainable, while being able to enforce hemodialysis and a blood filtration therapy to stability, the polysulfone film of the medical application excellent also in safety can be offered.

TECHNICAL FIELD

[Industrial Application] This invention relates to a polysulfone hollow fiber, and relates to the suitable medical-application polysulfone hollow fiber for hemodialysis and blood filtration especially aiming at the therapy of renal failure.

PRIOR ART

[Description of the Prior Art] Although the artificial kidney of current various kinds is used for the therapy of renal failure, these most are for removing the wastes in the blood which makes a urea representation by performing hemodialysis and blood filtration using a hollow fiber. Therefore, in order that blood may contact the film, as a membranous material, the safe material is used to living bodies, such as a cellulose, cellulose acetate, a polyacrylonitrile, polysulfone, polymethylmethacrylate, and an ethylene-vinylalcohol copolymer.

[0003] On the other hand, if there is much adhesion on film front faces, such as blood protein, in order that the dewatering capacity stabilized in stability is searched for for treating since hemodialysis and blood filtration need 4 to 5 hours therapy time amount, but dewatering capacity may decline with time, a hollow fiber adhesion of the corpuscle component which makes adhesion of blood protein or a platelet representation excelled [hollow fiber] in few anti-thrombus nature and biocompatibility is desired.

[0004] It is thought that it is useful to give a hydrophilic property to the film generally as a means to solve such a technical problem. For example, a membranous hydrophilic property is raised to JP,2-18695,B by making content in the inside of the film of a polyvinyl pyrrolidone into 5 to 70% in the film which consists of a polyvinyl pyrrolidone which are a hydrophobic giant molecule and a hydrophilic giant molecule. Although the method of raising biocompatibility and anti-thrombus nature is indicated, the hollow fiber internal surface which is the publication only about a membranous presentation ratio and becomes the most important for determining the anti-thrombus nature of a hollow fiber by which blood contacts directly and is used for medical application, and biocompatibility is not indicated at all.

[0005] the film which contains a hydrophilic giant molecule in JP,61-402,A or JP,62-38205,A on the other hand only at a compact layer side -- moreover, although the film with which the polyvinyl pyrrolidone was unevenly distributed in the internal-surface side of a hollow fiber is indicated by JP,4-300636,A, it is only the publication of a hydrophilic giant molecule existing in the section near the front face which both contacts the film front face, i.e., blood, itself, and the concrete publication about the property is not made at all.

EFFECT OF THE INVENTION

[Effect of the Invention] Since according to this invention hydrophilization of the film internal surface of a polysulfone hollow fiber is carried out by the polyvinyl pyrrolidone and the abundance has become 20% - 50%, adhesion of the protein to a hollow fiber internal surface, a platelet, etc. is controlled, and it is hard coming to start blinding. Therefore, since the stable dewatering capacity is maintainable, while being able to enforce hemodialysis and a blood filtration therapy to stability, the polysulfone film of the medical application excellent also in safety can be offered.

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] This invention aims at offering the polysulfone hollow fiber of the suitable medical application for hemodialysis and blood filtration excellent in anti-thrombus nature and biocompatibility.

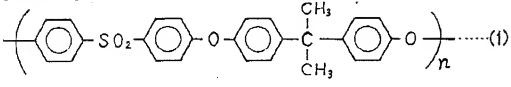
MEANS

[Means for Solving the Problem] In order to offer the medical-application hollow fiber excellent in anti-thrombus nature and haemocompatibility, this invention persons come to complete this invention wholeheartedly as a result of examination. That is, this invention is a hollow fiber which consists of polysulfone system resin and a polyvinyl pyrrolidone, and is the polysulfone hollow fiber of the medical application characterized by the abundance of the polyvinyl pyrrolidone in an internal surface being 20% or more and 50% or less.

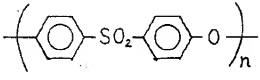
[0008] This invention is explained below at a detail. Although polysulfone system resin is especially the generic name of the high molecular compound which has sulfone association and it does not specify, when an example is given, the polysulfone system resin shown by following the (1) type or (2) formulas is marketed widely, since acquisition is also easy, it is desirable, and polysulfone resin with the chemical structure shown by (1) formula especially is good. The polysulfone resin with this structure is marketed by the trade name of you Dell from the Amoco performance products, and especially although some classes exist with polymerization degree etc., it is not scrupulous.

[0009]

[Formula 1]



(1)



(2)

[0010] Moreover, the polyvinyl pyrrolidone of various molecular weight is marketed by a plus boss's trade name for example, from insertion sequence Py, and a polyvinyl pyrrolidone can use the polyvinyl pyrrolidone of every molecular weight in this invention. Since the residual percentage of the polyvinyl pyrrolidone to the inside of the film becomes large so that molecular weight is large, a with a molecular weight of 300,000 or more polyvinyl pyrrolidone is used preferably.

[0011] The dryness-and-moisture type film production technique which is a technique generally known from before on the occasion of film production of a hollow fiber can be used. The solution which carried out dissolution mixing is used for the solvent which dissolves both polysulfone system resin and polyvinyl pyrrolidone in common as a film production undiluted solution for performing dryness-and-moisture type film production. Although it does not specify especially as this solvent, it is high, and since acquisition is also easy, solvents, such as N,N-dimethylacetamide, N, and N-dimethyl formamide, N-methyl pyrrolidone, and dimethyl sulfoxide, can also use solubility simple. N,N-dimethylacetamide is the most desirable when

safety, cost, etc. to the solubility and living body to polysulfone are considered especially. Although these solvents can be used of course independently, it can be used even if it mixes the solvent of the class beyond two sorts or it, in order to adjust the solubility which carries out a polymer pair.

[0012] Since film formation will become difficult if the concentration of this polysulfone system resin is too low, and film reinforcement becomes weak, or spinning nature will worsen if too high, or phenomena, like an aperture becomes small arise Although it is desirable that they are 15 - 20 % of the weight and further 16 - 18 % of the weight especially 12 to 25% of the weight, it can also make it high to make it lower than this range depending on the description of the hollow fiber which it is not limited to this range and made into the purpose.

[0013] A part of the polyvinyl pyrrolidone added in the film production undiluted solution remains in the film in the process in which the film is formed. Since the residual rate changes with the molecular weight and the spinning conditions of a polyvinyl pyrrolidone, although the optimal concentration of a polyvinyl pyrrolidone changes, generally its 1 - 20 % of the weight is good, and 3 - 10 % of the weight is still more preferably good [concentration] two to 15% of the weight preferably. Since a polyvinyl pyrrolidone becomes easy to remain in the film as molecular weight becomes large, the concentration may be low when the molecular weight of a polyvinyl pyrrolidone is large. For example, especially when the molecular weight of a polyvinyl pyrrolidone is 300,000 or more, it is desirable that it is 3 - 7 % of the weight one to 15% of the weight.

[0014] Since the polyvinyl pyrrolidone which remains in the film will decrease too much if lower generally than 1 % of the weight, the polyvinyl pyrrolidone which exists in a hollow fiber internal surface becomes 20% or less, hydrophilization becomes inadequate, adhesion of blood protein becomes intense, and the stable dewatering engine performance is no longer obtained. Moreover, since the viscosity of a film production undiluted solution will become high too much and film production will become difficult if higher than 20 % of the weight, the addition of a polyvinyl pyrrolidone is within the limits, and should be set [above-mentioned] up suitably.

[0015] Moreover, for the aperture control of a hollow fiber made into the viscosity control or the purpose of this film production undiluted solution, it is also possible to add nonsolvents, such as tetraethylene glycol, propylene glycol, ethanol, isopropyl alcohol, a glycerol, and water, and it can choose suitably according to the description of the hollow fiber made into the purpose about the class and an addition. What is necessary is for film production of a hollow fiber to extrude internal coagulation liquid, and to make it run the distance of 1m from 5cm, and to carry out the dipping of it and just to roll it round after that the back and into a coagulation bath, from a core part, at the same time it extrudes this film production undiluted solution from the sheath using the spinning port of a tube in orifice mold.

[0016] Although the liquid which made water the subject as internal coagulation liquid and coagulation bath liquid is used, in order to discover the description of the hollow fiber made into the purpose, the solvent of polysulfone resin and the mixed liquor of water can be used. It is that still more desirable one considers as 3,000 to 4,500 centipoise on the occasion of film production although it is desirable that it is the undiluted solution viscosity at the time of film production, and is 1,500 to 6,000 centipoise as for important one. That is, although the part is eluted into a coagulation bath at the time of film coagulation since a polyvinyl pyrrolidone is water solubility, it is because the spreading diffusion of a polyvinyl pyrrolidone is suppressed by making undiluted solution viscosity high and it becomes easy to remain in the film.

[0017] Although the mileage of the air section is still more important, when the dipping of the

hollow filament is carried out into a coagulation bath in the condition that it is not fully completed as the reason, membranous formation, i.e., coagulation, but the spreading diffusion of the polyvinyl pyrrolidone can still be carried out, it is because a polyvinyl pyrrolidone is eluted into a coagulation bath and a polyvinyl pyrrolidone stops remaining into the film.
[0018] Therefore, as for the film production undiluted solution extruded from the spinning port, it is desirable to fully have solidified, by the time a dipping is carried out into a coagulation bath, and it is desirable that time amount after a film production undiluted solution is extruded from a spinning port for that purpose until a dipping is carried out into a coagulation bath is 0.1 seconds or more and 0.3 more seconds or more. When for that a spinning rate is a part for 50m/, the distance of the air section is good to be about referred to as 8cm or more and 25 morecm or more. Moreover, although it is so desirable that it is not necessarily specified and enlarges about the upper limit, since it will become easy to generate the thread breakage if it enlarges not much, it is good that it is the range which does not exceed 100cm.
[0019] The hollow fiber by which the dipping was carried out to the coagulation bath rolls round, after rinsing in a wash bath further if needed. In order to remove a non-washed residual solvent, that what is necessary is for warm water etc. just to wash further, the obtained hollow fiber can make aperture hold-back agents, such as a glycerol, able to adhere if needed, and can also be dried. Thus, the polyvinyl-pyrrolidone abundance on the front face of the film had become 20% or more and 50% or less, the obtained hollow fiber was excellent in anti-thrombus nature and biocompatibility, and its film surface adhesion of protein, a platelet, etc. was also slight. This film demonstrates big effectiveness, in order to have the stable dewatering capacity and to treat hemodialysis, blood filtration, etc. to stability.
[0020] By the way, although the detail about the dewatering capacity stabilized why by making the abundance ratio on the front face of the film of a polyvinyl pyrrolidone into 20% or more being acquired is unknown Abundance required for the polyvinyl pyrrolidone which is the giant molecule of a hydrophilic property to cover the surface section of the polysulfone which is the hydrophobicity which is originally easy to adsorb protein etc., and hide it is 20% or more. Since hydrophilization of the film front face is fully carried out as the result, it is expected that the dewatering capacity by which adsorbent [of the protein on the front face of the film etc.] was weakened and stabilized is acquired.
[0021] Moreover, since a problem may crop up on safety in order that the engine performance is stable since hydrophilization of the film front face is further carried out if the abundance on the front face of the film of a polyvinyl pyrrolidone is larger than 50%, but on the other hand the danger that a polyvinyl pyrrolidone will be eluted in blood in the time of hemodialysis etc. may follow, as for the abundance of a polyvinyl pyrrolidone, it is desirable that it is 50% or less.
[0022] In addition, the abundance of the polyvinyl pyrrolidone on the front face of the film as used in the field of this invention say the abundance calculated from the nitrogen content and sulfur content in the film surface section for which blood be the abundance in the pole surface section in contact with the film, and it specifically asked with the X ray photon spectrum (X-ray photoelectron spectroscopy, henceforth, XPS), and when polysulfone resin be the structure of (1) type, it can ask by count by (3) types.
[0023]
[Equation 1]

ポリビニルピロリドン存在率（%）

$$= \frac{\text{窒素原子数} \times 111}{\text{窒素原子数} \times 111 \ + \ \text{硫黄原子数} \times 442} \times 100 \quad \cdots (3)$$

EXAMPLE

[Example] This invention is explained based on an example and the example of reference below at a detail.

[0025]

[Example 1] The homogeneity dissolution of the polysulfone resin (Amoco performance products, P-1700) 18 section, the polyvinyl-pyrrolidone (insertion sequence Py, plus boss K-90, molecular weight 360000) 5 section, and the N,N-dimethylacetamide 77 section was carried out. This undiluted solution had the viscosity of 3,800 centipoises at 45 degrees. Coincidence was made to breathe out this film production undiluted solution in the condition of having kept it warm at 45 degrees, making the N,N-dimethylacetamide water solution of 50% of concentration breathe out as internal coagulation liquid using the hollow spinning port of a tube in orifice mold. This undiluted solution was rolled round at the rate of back 50 m/min by which the dipping was carried out during the water bath of 50 temperature already kicked caudad 40cm.

[0026] The obtained hollow fibers were permeable ability 245 ml/Hr-m2, and [the bore of 0.195mm, the outer diameter of 0.310mm, and] mmHg, and the polyvinyl-pyrrolidone abundance in the film surface section for which it asked by XPS was 35%. The obtained hollow fiber is used and it is 2 0.02m of effective film surface products. Change was slight, when the mini module was created and aging of sink filtration velocity was seen for the cow plasma of total protein concentration 5.8 g/L in the state of the linear velocity of 1cm/second, and filtration pressure 200mmHg.

[0027] Furthermore, when the safety test was carried out based on dialysis mold artificial-kidney acknowledgement criteria to the obtained hollow fiber, they were all item success. Those results are shown in Table 1.

[0028]

[The example 1 of a comparison] The film production undiluted solution which carries out the homogeneity dissolution by the ratio of the polysulfone (P-1700) 18 section, the polyvinyl-pyrrolidone (K-90) 0.5 section, and the N,N-dimethylacetamide 81.5 section, and has the viscosity of 750 centipoises at 45 degrees was obtained. The hollow fiber was obtained like the example 1 using this film production undiluted solution except using internal coagulation liquid as 65% of N,N-dimethylacetamide water solution.

[0029] This hollow fiber was permeable ability 183 ml/Hr-m2, and [the bore of 0.208mm, the outer diameter of 0.327mm, and] mmHg, and the polyvinyl-pyrrolidone abundance on the front face of the film was 18%. The same trial as an example 1 was carried out using the obtained hollow fiber. Although the safety test was passed, the dewatering engine performance by which aging of filtration velocity was stabilized greatly was not obtained.

[0030] Those results are shown in Table 1.

[0031]

[The example 2 of a comparison] The homogeneity dissolution was carried out by the ratio of the

polysulfone (P-1700) 18 section, the polyvinyl-pyrrolidone (K-15) 25 section, and the N,N-dimethylacetamide 57 section, and the film production undiluted solution of 7,600 centipoises was obtained at 45 degrees. The hollow fiber was obtained like the example 1 using this film production undiluted solution except using internal coagulation liquid as water.

[0032] This hollow fiber was permeable ability 370 ml/Hr-m2, and [the bore of 0.192mm, the outer diameter of 0.298mm, and] mmHg, and the polyvinyl-pyrrolidone abundance on the front face of the film was 55%. When the same trial as examples 2 and 3 was carried out using the hollow fiber obtained in the example 4 of reference, aging of filtration velocity became a rejection by the item of the ultraviolet absorption spectrum in a safety test, although the dewatering engine performance stabilized small was obtained.

[0033] Those results are shown in Table 1.

[0034]

[Table 1]

使用した中空糸膜	ろ過速度（ml／Hr・m^2・mmHg）					溶出物試験
	15分後	1時間後	2時間後	3時間後	4時間後	
実施例1	22．5	23．4	22．3	21．8	21．3	合格
比較例1	18．4	17．8	16．2	14．4	12．6	合格
比較例2	24．7	23．5	23．7	22．9	22．9	不合格

[Translation done.]